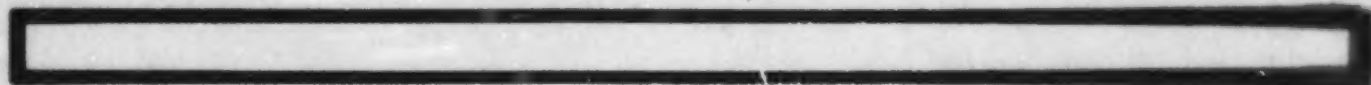


PB83-243394

**Pulmonary Dosimetry of
Nitrogen Dioxide in Animals and Man**

**(U.S.) Health Effects Research Lab.
Research Triangle Park, NC**

Jul 83



**U.S. Department of Commerce
National Technical Information Service**

NTIS

TECHNICAL REPORT DATA

(Please read instructions on the reverse before completing)

1. REPORT NO. EPA-600/D-83-091		3. RECIPIENT'S ACCESSION NO. pgg 3 243394	
4. TITLE AND SUBTITLE Pulmonary Dosimetry of Nitrogen Dioxide in Animals and Man		5. REPORT DATE 1983	
7. AUTHOR(S) E.J. Miller, J. H. Overton, E.T. Myers, and J.A. Graham		6. PERFORMING ORGANIZATION CODE	
9. PERFORMING ORGANIZATION NAME AND ADDRESS Toxicology/Inhalation Branch Health Effects Research Laboratory US Environmental Protection Agency Research Triangle Park, NC 27711		8. PERFORMING ORGANIZATION REPORT NO.	
12. SPONSORING AGENCY NAME AND ADDRESS Office of Research and Development Health Effects Research Laboratory US Environmental Protection Agency Research Triangle Park, NC 27711		10. PROGRAM ELEMENT NO.	
		11. CONTRACT/GRANT NO.	
		13. TYPE OF REPORT AND PERIOD COVERED	
		14. SPONSORING AGENCY CODE EPA-600/11	
15. SUPPLEMENTARY NOTES			
16. ABSTRACT Using a general mathematical model formulation for the transport of gases in the lungs, we studied the regional pulmonary deposition of nitrogen dioxide (NO ₂) in man, rabbits, guinea pigs, and rats. The model formulation utilizes lung morphometric data and includes parameters reflecting physiochemical properties of NO ₂ , ventilatory patterns, and chemical reactions of NO ₂ with components of the protective layer linings of the lungs. Sensitivity of model predicted doses to changes in some of the above parameters are discussed as well as qualitative comparisons between animals and man in the shape of the dose curves.			
17. KEY WORDS AND DOCUMENT ANALYSIS			
a. DESCRIPTORS		b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group
18. DISTRIBUTION STATEMENT Release to Public		19. SECURITY CLASS (This Report) Unclassified	21. NO. OF PAGES 14
		20. SECURITY CLASS (This page) Unclassified	22. PRICE

EPA-600/D-83-091
July 1983

PULMONARY DOSIMETRY OF NITROGEN DIOXIDE IN ANIMALS AND MAN

by

E. J. Miller and J. A. Graham
Inhalation Toxicology Division
Health Effects Research Laboratory
U.S. Environmental Protection Agency
Research Triangle Park, NC 27709

J. H. Overton and E. T. Myers
Northrop Services, Inc.
Research Triangle Park, NC 27711

HEALTH EFFECTS RESEARCH LABORATORY
OFFICE OF RESEARCH AND DEVELOPMENT
U.S. ENVIRONMENTAL PROTECTION AGENCY
RESEARCH TRIANGLE PARK, NC 27711

REPRODUCED BY
NATIONAL TECHNICAL
INFORMATION SERVICE
U.S. DEPARTMENT OF COMMERCE
SPRINGFIELD, VA. 22161

NOTICE

This document has been reviewed in accordance with U.S. Environmental Protection Agency policy and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

PULMONARY DOSIMETRY OF NITROGEN DIOXIDE IN ANIMALS AND MAN

E.J. MILLER,¹ J.H. OVERTON,² E.I. MYERS,² and J.A. GRAHAM¹

¹Toxicology Branch, Inhalation Toxicology Division, Health Effects Research Laboratory, Environmental Protection Agency, Research Triangle Park, North Carolina 27711 (USA)

²Health Effects Research, Northrop Services, Inc., P.O. Box 12313, Research Triangle Park, North Carolina 27709 (USA)

ABSTRACT

Using a general mathematical model formulation for the transport of gases in the lungs, we studied the regional pulmonary deposition of nitrogen dioxide (NO_2) in man, rabbits, guinea pigs, and rats. The model formulation utilizes lung morphometric data and includes parameters reflecting physicochemical properties of NO_2 , ventilatory patterns, and chemical reactions of NO_2 with components of the protective layer linings of the lungs. Sensitivity of model predicted doses to changes in some of the above parameters are discussed as well as qualitative comparisons between animals and man in the shape of the dose curves.

INTRODUCTION

Major factors affecting the uptake of nitrogen dioxide (NO_2) in the respiratory tract of animals and man are the morphology of the respiratory tract, the route of breathing, the depth and rate of breathing, physicochemical properties of NO_2 , the physical processes which govern gas transport, and the physicochemical properties of the aqueous material on the surface of the airways or gas exchange units. In estimating NO_2 concentrations responsible for observed pulmonary effects, nasopharyngeal removal of the pollutant is important. Removal of NO_2 in this region serves to lessen the dose to more sensitive pulmonary tissue. Upper airway studies on NO_2 have been conducted using cats [1]. Nasopharyngeal uptake of NO_2 in man during normal respiration versus exercise and for different breathing routes needs to be studied. Such

studies provide appropriate initial or boundary concentrations for theoretical models which examine gas transport and removal in the lower airways.

Evaluation of the health effects associated with NO_2 exposure requires integration of information from epidemiological, human clinical, and animal toxicological studies. This integration can be better facilitated by an awareness of pulmonary dosimetry comparisons between laboratory animals and man. The current study examines some of these comparisons and identifies limitations that currently exist on their use. Hopefully, it will be made clear that one should consider pulmonary dosimetry modeling as a dynamic process rather than as a static one.

METHODS

Pulmonary Deposition Model

Since much of the basis for the model has been described previously [2,3], only a brief description of the model will be given. The respiratory tract model or the lung model structure consists of a series of sequential generations or zones. Associated with each generation or zone is a set of parallel right circular cylinders, the interior of which is the airway lumen (see e.g., [4]). The number and dimensions of the cylinders are based on the morphometric data of Weibel [5] for man and Kliment [6] for guinea pigs, rabbits, and rats. A thin liquid layer representing mucus or surfactant coats the interior wall of each cylinder, whereas the wall corresponds to tissue. Applied to this model is a differential equation which takes into account the convection and diffusion of NO_2 in the lumen and diffusion and chemical reaction with mucous components by NO_2 in the thin liquid layer.

Numerical analysis techniques

A multistep procedure in finite difference form was used to obtain solutions to the differential equation of continuity (mass balance). The respiratory cycle was divided into a sequence of time steps and each step was divided into two fractional steps [7] to facilitate the numerical solution. In the first fractional step, convection and diffusion (effective diffusion coefficient based on [8]) were included in describing the effects of transport in the airways. Diffusion and chemical reactions in the liquid layers were considered in the second step to account for the removal of NO_2 from the lumen of an airway and for the uptake of NO_2 by tissue walls.

The numerical formulation was tested by using simple "lung" geometries for which the differential equation has known analytical solutions. Comparison of simulated results with the analytical solutions demonstrated the correctness of the formulation.

Chemical reaction scheme

There is less certainty as to the appropriate reaction scheme for NO_2 and various components in mucus or in surfactant than there is, for example, for ozone (O_3). While it appears that NO_2 should react with many of the same constituents of the protective layers of the lungs as does O_3 , it is possible that such reactions are not diffusion controlled, as is the case for O_3 [9]. Definitive studies are critically needed on the types and rates of reaction of NO_2 with various free amino acids, lipids, carbohydrates, etc. We are currently assessing information available from more recent studies [10-12] to extract possible reaction components in addition to those identified previously [13-15]. For now, we have chosen to use for NO_2 the same mucous production scheme as was used for O_3 [2], but one-half of the O_3 reactant production rates. Also, recognizing the unknown reactivity of NO_2 , we will examine the sensitivity of the predicted tissue dose to various values of NO_2 reactant production rates.

Henry's law for NO_2

The determination of Henry's law constant (H) for NO_2 has been the subject of several investigations and the resultant values are spread over an order of magnitude range [16]. The value we use ($H=9628$ atmos./mole fraction) and the method of obtaining it by an extrapolation to 37°C is taken from [16,17]

RESULTS AND DISCUSSION

Sensitivity of dose to Henry's law constant

As indicated earlier, considerable variability exists among available values for Henry's law constant for NO_2 . While the model analyses to be discussed subsequently employed a value of $H=9628$ atmos./mole fraction based upon [16,17], Figure 1 illustrates the effects of three different values of Henry's law constant on the tissue dose of NO_2 using one half the reactant production rate of O_3 (which is symbolized by $K = .5K_0$). The values of H used were the nominal value of 9628, one-half and twice this value.

Quantitatively, the results can be very different as can be seen for the NO_2 tracheal concentration of $800 \mu\text{g}/\text{m}^3$. There is no penetration of NO_2 to the tissue prior to the 12th generation for the two largest values of H. In those generations where penetration occurs, for all three values of H the dose values can differ by as much as a factor of 20. On the other hand, there is very little difference at the 19th or 20th generation where the curves for the three values of Henry's law constant cross. Qualitatively, for a given NO_2 concentration, the curves are essentially the same; peaks or valleys occur at the same generation irrespective of H, and the maximum tissue dose occurs at

the 12th generation. Similar qualitative results are obtained for a larger reaction rate, $K = .5K_0$ (not shown); however, some details differ. For

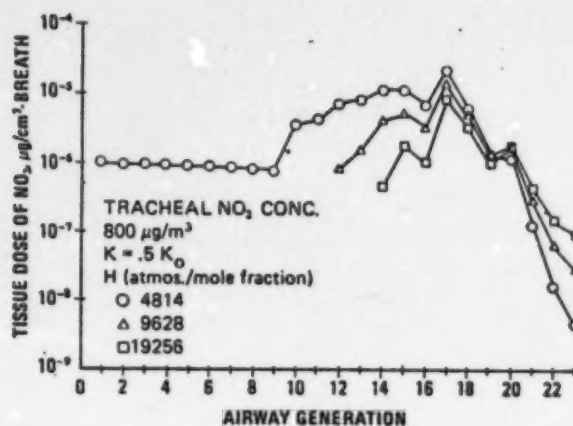


Figure 1. Influence of the value of Henry's law constant, H , on the tissue dose of NO_2 in the lungs of man. Simulations used a tidal volume of 500 ml and a respiratory frequency of 15 breaths/min.

example, NO_2 does not penetrate to the tissue until the 12th generation. Generally, prior to the alveolar region, as H increases the tissue dose decreases; whereas within the alveolar region the converse is true.

Sensitivity of dose to reactant production rates

As previously indicated, the reaction scheme for NO_2 in the mucus or surfactant layers is uncertain. Nevertheless one can obtain an idea as to the effect of chemical reactions by using the instantaneous reaction scheme and varying the reactant production rate. Results of simulations of this type are illustrated in Figure 2 for the NO_2 lost by the lumen (Panel A) and the tissue dose of NO_2 (Panel b) for each generation for a tracheal NO_2 concentration of 800 μg/m³. K_0 indicates a reference reaction production rate the same as that used for O_3 . The factor in front of K_0 refers to the fraction of K to which the reactant production rate has been reduced. Thus, the results are plotted of what may be considered extremes for the uptake of NO_2 - no chemical reactions ($0K_0$) and an upper limit, as represented by the O_3 rate ($1K_0$).

From Figure 2A it can be seen that the uncertainty of chemical reactions gives rise to a factor of five uncertainty in the uptake of NO_2 in the trachea (0th generation). The uncertainty decreases to insignificance by generation 14 or 15, and for the remaining generations (16-23) the uptake is not sensitive to the variation in the NO_2 reactant production rate.

Only a fraction of the NO_2 lost by the lumen may reach the tissue walls. This amount, the tissue dose, is plotted in Figure 2B. A comparison of Figures 2A and 2B illustrates the protective nature of the mucous layer; with our values for the chemical reactions, no NO_2 reaches the tissue wall before the 12th generation (Fig. 2B). For the reference curve ($1K_0$) over 14 times as much NO_2 is lost by the lumen (in the 14th generation) as penetrates to the tissue wall. This difference ceases at the 17th generation where, in our model, the protective layer has no reactants. From generation 17-23 the wall uptake is not only insensitive to the chemistry in the previous generations, but is the same as is lost by the lumen (Fig. 2A).

Tissue dose curves in man and animals with normal respiration

Since the tissue dose curves presented in Figure 2B for $0.5K_0$ and $1K_0$ as a function of airway generation in the human lung are qualitatively similar, we chose to examine the tissue dose curves for NO_2 in man compared to the curves in animals using a common value of $0.5K_0$.

For the above tracheal NO_2 concentration, estimates for the dose delivered to the tissue in various generations of the human lung (Δ — Δ in Fig. 2B) predict that NO_2 does not penetrate to the tissue prior to the 12th generation. This region represents one of the first branchings of the conducting airways near the terminal bronchioles. The dose curve then increases sharply, dips at the 16th generation, then reaches an absolute maximum at the first generation of respiratory bronchioles (generation 17). Proceeding distally there is a rapid fall in the dose of NO_2 delivered to the tissue, due in large part to the correspondingly rapid increase in lung surface area. Non-zero tissue doses in the conducting airways are approximately 3 to 15 times smaller than the peak dose, while average alveolar region (generations 20-23) doses are on the order of a 100-fold less.

The morphometric data utilized to obtain tissue dose curves in the lungs of rats, guinea pigs, and rabbits [6] is classified according to "morphometric zone" rather than airway generation so that several human airway generations may correspond to a morphometric zone in these animal species. Predicted tissue doses of NO_2 in the lungs of these animal species are shown in Figure 3A. The shape of the dose curves for guinea pigs and rabbits appear to be more similar to each other than to the dose curve for rats. It is interesting that the predicted dose curve for rats is relatively flat over major regions of the tracheobronchial tree. Also, alveolar ducts are predicted to be the region for the maximal tissue dose of NO_2 in rats, whereas the maximal dose region is the last generation of bronchioles in guinea pigs and rabbits. This

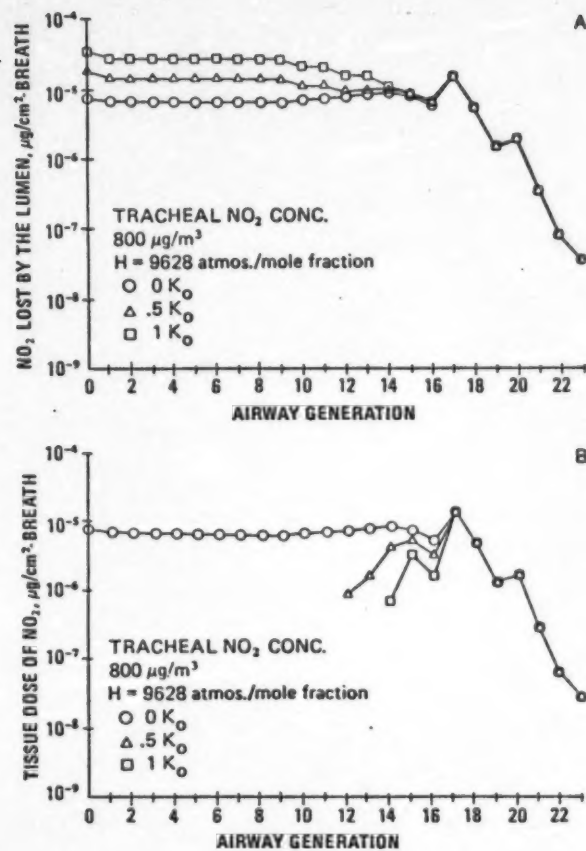


Figure 2A. NO₂ lost by the airway lumen as a function of airway generation in the human lung. B. Predicted NO₂ tissue dose curves in the lungs of man. Simulations used a tidal volume of 500 ml and a respiratory frequency of 15 breaths/min.

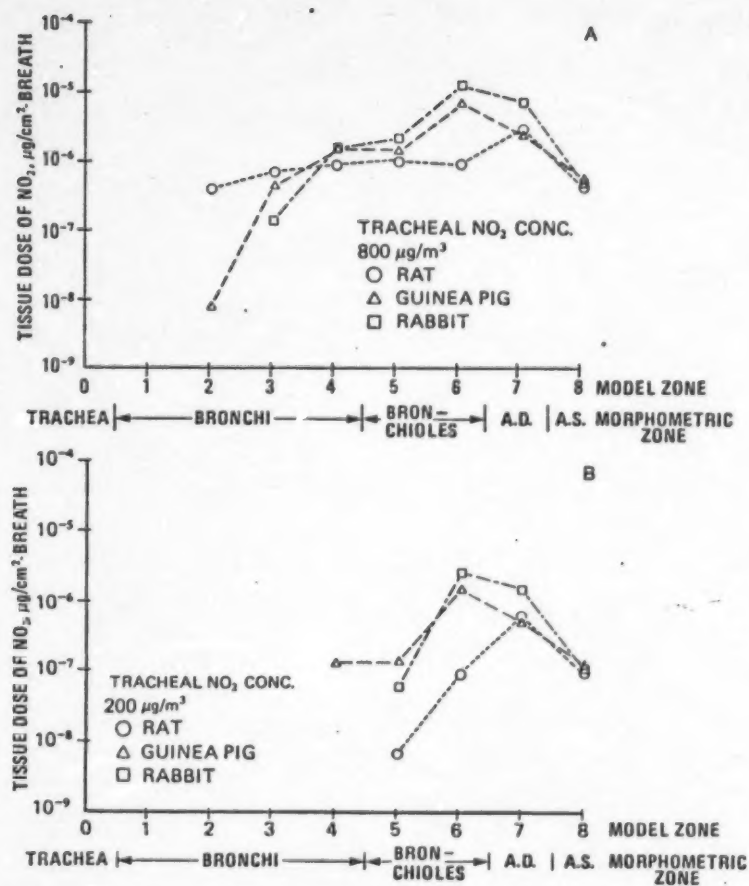


Figure 3. Predicted NO_2 tissue dose curves in the lungs of rats, guinea pigs, and rabbits for various morphometric regions. Panels A and B correspond to simulations for 800 and 200 $\mu\text{g}/\text{m}^3$, respectively. For rats, guinea pigs, and rabbits, tidal volumes of 0.95, 1.8, and 21 ml and breathing frequencies of 105, 90, and 50 breaths/min., respectively, were used. Alveolar ducts and sacs are represented by A.D. and A.S., respectively.

shift is probably reflective of the model formulation concerning the transition from mucous lined to surfactant lined regions of the lung and of the lack of respiratory bronchioles in the rat. Unlike the more than 100-fold difference seen in man between the peak dose and the dose in more distal regions, a similar comparison for the dose curves in the animal lungs indicate only about a 10-fold difference.

Figure 3B depicts predicted tissue dose curves in rat, guinea pig, and rabbit lungs for a tracheal NO_2 concentration of $200 \mu\text{g}/\text{m}^3$ (0.11 ppm). At this lower concentration the dose patterns are now more similar in the conducting airways. Although not shown, penetration of NO_2 to conducting airway tissue in man is not predicted for an inhaled tracheal concentration of $200 \mu\text{g}/\text{m}^3$ (0.11 ppm). More definitive quantitative data on the biochemical composition of the mucous layer in man and animals is clearly needed before one can resolve some of the apparent differences in conducting airway dose curves.

Effects of tidal volume on NO_2 dose in man

Tidal volume averages approximately 500 ml in adults during normal respiration. However, various levels of exercise result in increased tidal volume and respiratory frequency. Figure 4 gives the predicted percent uptake of NO_2 by mucus and by airway walls for various tidal volumes. There is a decline in the percent uptake of NO_2 by mucus that is paralleled by an increase in the percent uptake of NO_2 by respiratory airway tissue as tidal volume increases from 500 ml to 2250 ml. Percent uptake of NO_2 by conducting airway tissue remains relatively constant at a low level. For any given tidal volume, the vast majority of the percent uptake of NO_2 is associated with respiratory tissue. Although not shown, the maximal tissue dose of NO_2 increases by a factor of 2 to 3 as tidal volume increases over the range depicted in Figure 4. On the other hand the total O_3 absorbed by the tissue increases by a factor of 6 to 7.

Lung morphometric data and mathematical models

One of the major concerns in modeling the uptake of pollutants is that the respiratory tract model be representative of real lungs. The degree to which the tract must be faithful has yet to be determined; however, a comparison of the several respiratory tract models available indicates a wide variation in supposedly equivalent dimensions as well as in structure. An example of this is the types of models used: Weibel's [5] twenty-four generation based and Landahl's and Kliment's [6] eight morphometric zone based models. The appropriateness of comparing the results of simulations using the two types of models is questionable in view of the following.

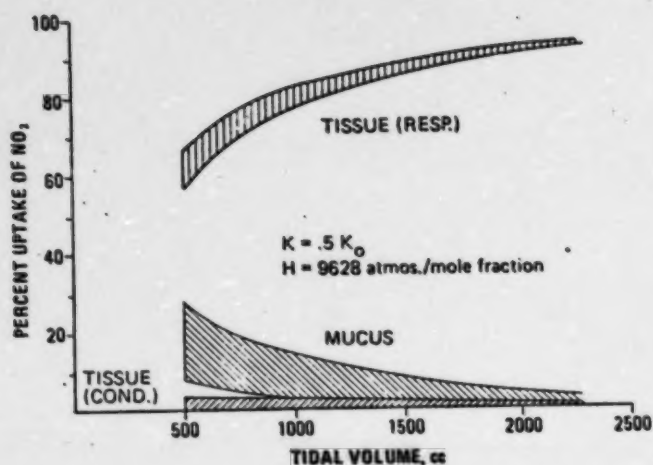


Figure 4. Uptake of NO_2 by mucus and airway walls of man as a function of tidal volume. Results from simulation using tracheal NO_2 concentrations of 200 and 800 $\mu\text{g}/\text{m}^3$ form the lower and upper bounds, respectively, for the uptake by tissue regions, while the reverse is true for the uptake by mucus.

Table 1 indicates the discrepancy between a "collapsed" Weibel's and Landahl's model for man. Weibel's generations have been lumped to create regions or zones that approximate those of Landahl. In doing so we have preserved the total number of airways per zone, total volume, cross sectional area, length and air-tissue interface surface area. The radius of a "created" lumen in a given zone is based on the assumption that it is a right circular cylinder with the length of the accumulated generations and radius commensurable with this length, the total volume, and number of lumen assigned to the given zone.

The values in the table range from less than 0.2 to greater than 6.0. These differences are important since the parameters whose ratios are tabulated are necessary and key inputs for our model. Thus, we not only question whether or not the two respiratory tract models (either in zone or generation form) represent the same lung, but also if either lung model is a valid representation of the human lung. For modeling purposes, improved data is needed to define not only the structure or geometry of the respiratory tract but also the dimensions of the needed parameters.

TABLE 1

A comparison of lung models by Landahl and Weibel.

Zone	REGION	GENER- ATIONS	$\frac{N_L}{N_C}$	$\frac{V_L}{V_C}$	(1)	(2)	(3)	(4)
					$\frac{A_L}{A_C}$	$\frac{l_L}{l_C}$	$\frac{S_L}{S_C}$	$\frac{R_L}{R_C}$
0	Trachea	0	1.0	0.8	0.8	0.9	0.8	0.9
1	Bronchi I	1	1.0	0.9	0.7	1.4	1.1	0.8
2	Bronchi II	2	3.0	1.0	0.7	1.6	2.3	0.5
3	Bronchi III	3-6	0.8	0.4	1.0	0.4	0.7	1.1
4	Bronchi IV	7-11	0.2	0.3	1.4	0.2	0.2	2.7
5	Bronchioles I	12-16	0.4	0.5	2.2	0.3	0.7	2.1
6	Bronchioles II	17-19	0.2	0.2	0.6	0.4	0.2	1.8
7	Ducts	20-22	3.5	0.2	2.4	0.1	0.5	0.8
8	Sacs	23	6.2	1.2	3.1	1.0	1.2	0.7

L = Landahl as cited in [6]; C = Weibel's model "A" collapsed to regions [5]
 N = number of airways, V = total volume, A = total cross sectional area,
 l = length of region, S = surface area, R = radius of airway.

(1) $A_C \equiv V_C/l_C$. (2) l_C = Accumulative sum of airway length in a region.

(3) $S_L \equiv 2\pi R_L \cdot l_L \cdot N_L$, S_C = Accumulative surface area of region.

(4) $R_C \equiv \sqrt{A_C/(\pi \cdot N_C)}$.

REFERENCES

- 1 M. Corn, N. Kotsko and D. Stanton, *Ann Occup. Hyg.*, 19 (1976) 1-12.
- 2 F.J. Miller, D.B. Menzel and D.L. Coffrin, *Environ. Res.*, 17 (1978) 84-101.
- 3 F. Miller in S.D. Lee and J.B. Mudd (Eds.) *Assessing Toxic Effects of Environmental Pollutants*, Ann Arbor Science, Ann Arbor, 1979, Ch. 14, pp. 263-286.
- 4 R. Hoffman, *Z. Ges Hyg. Ihre Grenzgebiete*, 18 (1972) 890-894.
- 5 E.R. Weibel, *Morphometry of the Human Lung*, Academic Press, New York, 1963, p. 303.
- 6 V. Kliment, *Folia Morphol.* 21 (1973) 59-64.
- 7 N.N. Yanenko, *The Method of Fractional Steps*, Springer-Verlag, New York, 1971, p. 117.
- 8 P.W. Scherer, L.H. Shendelman, N.M. Green and A. Bouhuys, *J. Appl. Physiol.*, 38 (1975) 719-723.
- 9 D.B. Menzel, in W.A. Pryor (ed), *Free Radicals in Molecular Biology and Pathology*, Vol. II, Academic Press, New York, 1976, pp. 181-202.
- 10 T.F. Boat and P.W. Cheng, *Fed. Proc.*, 39 (1980) 3067-3074.
- 11 M.J. Reasor, G.K. Adams III, D.F. Proctor, and R.J. Rubin, *J. Appl. Physiol.* 45 (1978) 182-189.
- 12 S.C. Sahu, A.K. Tanswell and W.S. Lynn, *Lung*, 158 (1980) 143-150.
- 13 R.W. Lewis, *Lipids*, 6 (1971) 859-861.
- 14 J.L. Potter, L.W. Matthews, J. Lemm and S. Spector, *Ann. N.Y. Acad. Sci.*, 106 (1963) 692-697.
- 15 R.D. Marshall, *Ann. Rev. Biochem.*, (1972) 673-702.

- 16 S.E. Schwartz and W.H. White, Equilibrium Solubility of the Nitrogen Oxides and Oxyacids in Aqueous Solution, BNL-27102, Brookhaven National Laboratory, Upton, New York, 1980, pp. 5-34.
- 17 S.E. Schwartz, Equilibria in the Nitrogen Oxide - Nitrogen Oxyacid-Water System, BNL-27827R, Brookhaven National Laboratory, Upton, New York, 1980, pp. 1-15.